Center for Environmental Health *in Northern Manhattan*

MAILMAN SCHOOL OF PUBLIC HEALTH
Columbia University
Director: Regina Santella

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Lead Exposure during Synaptogenesis Alters Vesicular Proteins and Impairs Vesicular Release: Potential Role of NMDA Receptor–Dependent BDNF Signaling

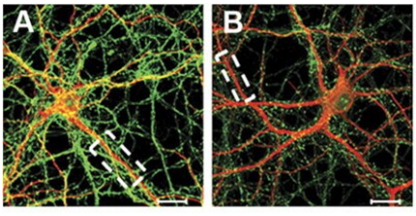
It is well known that lead exposure during childhood causes many negative health effects, including developmental delays and learning disorders. Recent studies have shown that lead exposure may reduce brain volume and impact presynaptic neurotransmitter release. Little is known, however, about how exactly lead acts in the brain to cause these effects.

Dr. Tomás Guilarte, who recently joined Columbia University Mailman School of Public Health as chairman of the Department of Environmental Health Sciences, and colleagues from Johns Hopkins Bloomberg School of Public Health recently conducted research to understand how these observed effects arise. The researchers examined a possible mechanism through which lead interferes with important processes in the brain that are related to neuron growth and survival. Their recently published paper, entitled *Lead Exposure during Synaptogenesis Alters Vesicular Proteins and Impairs Vesicular Release: Potential Role of NMDA Receptor–Dependent BDNF Signaling,* describes their findings (*Toxicol. Sci. (2010) 116 (1): 249-263).*

In this study, the researchers examined hippocampal neurons as they were forming new synapses. Their goal was to characterize the effect of lead on presynaptic active zones (PAZ) and vesicular release, both components of presynaptic functioning. They used hippocampal samples from rats. Lead acetate was added to the feeding medium given to the experimental group, but not the control group. The researchers then used a variety of methods to examine neurons harvested five days after exposure. These included cell viability assays, ELISAs (to examine brain-derived neurotrophic factor (BDNF) release), Western blotting, immunocytochemistry analysis of fixed cells and live imaging of vesicular release using the dye FM 1-43. (*continued on p.3)*

Lead exposure decreases the presynaptic protein synaptophysin, which is important for neurotransmitter release.

Panel A = control neuron; Panel B = lead-exposed neuron



WE ACT Update: NYC Lead Poisoning Outreach Campaign

Even though lead-based paint and leaded gasoline were outlawed approximately three decades ago, housing-related lead exposure continues to be a widespread problem in New York City. This is largely due to chipping lead paint that has not been removed from much of the aging housing stock in lower income neighborhoods. Initially, leaded paint was more expensive, and was used by middle to higher income families. Currently, however, lead poisoning is a problem that predominantly affects lower income communities.

In New York City, there are several exceptions to this trend. Children that live in several higher income neighborhoods, such as Gramercy, Chelsea, and Greenwich Village, have shown high levels of lead exposure in laboratory tests. The source of this is not completely understood, but it is related to gut renovations of historically preserved housing facilities, a process that stirs up lead dust. It is thought that children may be exposed in their homes, schools, or playgrounds.

However, the fact remains that the majority of children affected by lead exposure and its harmful health impacts live in low-income neighborhoods in what is called NYC's "lead belt". This area includes the South Bronx, Northern Manhattan, Bedford -Stuyvesant, and parts of Queens. WE ACT for Environmental Justice has a long history of conducting community outreach regarding household lead exposure in these communities. They recently expanded their work in this area by forming a partnership with the Children's Hospital at Montefiore. By collaborating with Project Director Dr. John Rosen, who is Professor of Pediatrics and Head of the Environmental Science Department at Montefiore, they have expanded their outreach to also include lead testing.

The two main goals of the project are to test housing stocks for lead, and to teach parents how to collect samples for testing themselves. An EPA-trained WE ACT staff member, Ana Parks, conducts home visits to initiate relationships with community members. She begins by showing parents the simple process through which samples are collected. First, parents identify the area where their children spend the most time. Then, a 2'x2' area is marked off and wiped down completely with a baby wipe. The wipe is then deposited into a clean beaker, packaged, and sent to a laboratory for testing. After Ms. Parks collects a sample and explains the process, parents then collect a second sample from an adjoining 2'x2' area.

Collecting paired samples has several benefits. First of all, it allows for comparison of sample data, to identify potential difficulties the parents are having with sample collection. Additionally, it engages the parents more deeply in the process, increasing the likelihood that they will stay engaged in follow-up to sampling. Paired samples are collected for a section of floor and windowsill. Lead paint is frequently left on windowsills, even when it has been removed from the walls of a home, so it is important to test both areas.

After samples have been collected, they are sent to a private lab. Parents are educated about this process as well, which is inexpensive and provides quick results. In total, parents usually wait about two weeks to receive the results on their samples. After the results have been received, Dr. Rosen reviews them. If lead levels in a home's samples are higher than the EPA maximum limit of 40 parts per billion (ppb), he takes blood samples of those living in the home, and then identifies an appropriate treatment plan. Families then receive a consultation, during which they are advised about their potential options to reduce their lead exposure. For example, when children are found to have blood lead levels of 10 to 20 µg/dL. Dr. Rosen talks with them about Local Law 1 which states that landlords are required to take steps to remediate lead levels. He then helps them plan how to pursue their rights under this law. Additionally, he lets them know about the Lead Safe House, which has temporary housing facilities for families that must vacate their homes while renovations for lead remediation are underway. When lead levels are between 15 and 20 µg/dL, Dr. Rosen involves the NYC Department of Health in pursuing remediation. For higher blood lead levels, he will also recommend a drug-based treatment plan to reduce the effects of lead exposure.

It is an unfortunate fact that lead exposure continues to be a serious problem in New York City. WE ACT has collected samples with lead levels as high as 4000 ppb. However, through this project, WE ACT is working to provide families with the resources and information they need to reduce their lead exposures. One mother who has participated in the project was shocked and saddened to discover that her five young children had been exposed to high levels of lead in their home. As a Spanish speaker with limited English proficiency, she initially felt overwhelmed by the barriers she faced in seeking help to address the situation. However, through the education and support provided by WE ACT, she has been able to access available resources and feels empowered to take action on behalf of her family's health.

Faculty Pilot Project: Aberrant microRNA and AFB1-, PAH-albumin

Dr. Jing Shen, Assistant Professor at Columbia University Mailman School of Public Health's Department of Environmental Health Sciences, was recently awarded an NIEHS Center pilot project grant. Aflatoxin B1 (AFB1) and polycyclic aromatic hydrocarbons (PAHs)-albumin adducts measured in human plasma are ideal surrogate biomarkers to indicate chronic carcinogen exposures. Both AFB1 and PAHs are genotoxic carcinogens that require metabolic activation to produce DNA damage leading to the development of hepatocellular carcinoma (HCC). Although the liver is not the first organ exposed to AFB1 and PAH, it is the place where they are bio-transformed. Previous studies conducted in cancer cell lines have shown that exposure to AFB1/PAHs and their biotransformation may result in a broad spectrum of gene expression changes in various biological pathways. MicroRNA (miRNA) alterations play a critical role in modulating gene and protein expression. Several miRNAs with oncogenic characteristics are significantly up-regulated in HCC tumor tissues, including miR-17-92, miR-21, miR-181b, miR-221, and miR-222 etc. Until now, no human HCC study has been conducted to evaluate miRNA expression profiles among tissues and relevant plasma samples in conjunction with information on exposure to AFB1 and PAHs.

The goal of the current study is to identify a panel of plasma miRNA markers to differentiate HCC cases from controls and their relationship to AFB1 and PAHs exposures. The study investigators hypothesized that oncogenic miRNA expression is up-regulated in HCC tumor tissues and pre-operative plasma, and the over-expression is even more significant for cases with high levels of AFB1 and PAHs exposure. They will examine the miRNA expression profiles in target HCC tumor tissues and adjacent non-tumor tissues. They will distinguish HCC-specific miRNA expression by comparing pre-operative plasma from HCC cases and matched controls, as well as pre- and post-operative plasma samples from the same cases. Finally, they will evaluate whether AFB1 and PAHs exposures display significant correlations with miRNA up-regulation in an independent set of HCC cases and age, gender, ethnicity matched controls. This pilot study will provide preliminary results for the role of miRNA up-regulation on AFB1 and PAHs exposures in determining HCC development. It may improve clinical early diagnosis and prognostic prediction of liver cancer.

Lead Exposure During Synaptogenesis *(Continued from p. 1)*

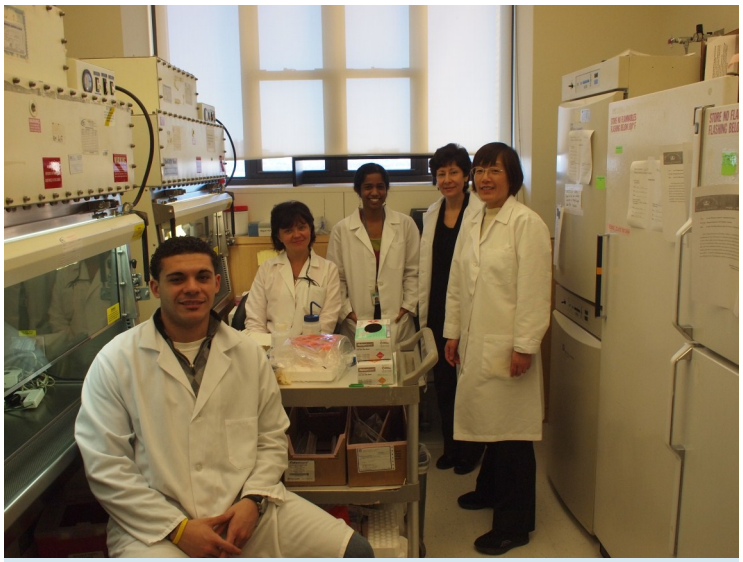
The study's findings suggest that the presynaptic effects of lead are actually related to interruption of the post-synaptic activity of N-methyl-D-aspartate receptors (NMDAR). This was shown to be associated with a subsequent decrease in the release of BDNF, which is responsible for signaling pre-synaptic neurotransmitter release, and is important for pre-synaptic plasticity (the ability to form new synapses). Therefore, when this retrograde signaling pathway is inhibited, neuronal growth and new synapse development are also impaired.

This is the first study to present evidence for a mechanism through which this environmental toxin acting at post-synaptic NMDA receptors in the brain is able to interrupt presynaptic processes that are fundamentally important to healthy, normal brain development.

Additionally, the implications of this research are important for the public. While lead exposure has been reduced significantly in recent years, environmental exposures to this toxin continue to occur more frequently than might be expected. Exposure comes from sources such as residual lead paint in older homes and lead-containing products imported from countries with less stringent restrictions on its use. When exposure occurs early in life, children are at risk of developmental delays that may affect them for their entire life. Dr. Guilarte reports that there is some good news, however. His research also shows that by exposing developing animals to increased mental stimulation through environmental enrichment, the effects of lead exposure can be reversed. Parents can empower themselves by proactively planning activities for their children such as physical exercise, and attending public events such as concerts and museums. New York City provides a variety of inexpensive opportunities for environmental enrichment that parents can take advantage of.

Biomarkers Core Facility Update

The Biomarkers Core Facility provides a centralized infrastructure to serve the needs of Center members and other researchers performing population-based studies. The main tasks of the facility are to receive, process, inventory, and store biological specimens and distribute them to researchers. This dynamic process requires a high level of efficiency and accuracy. To that end, the Core facility recently worked with the Statistical Analysis Center to develop a new database that is highly flexible and able to accommodate a diverse range of research projects. The database allows samples to be linked with related information available from questionnaires and surveys through a unique sample Core Facility specimen ID number. In total, the Core has 998,371 products in its database. Currently, the biological specimens from 38 various research projects are being processed and inventoried in the facility; over 70 projects have samples stored. Core manager Irina Gurvich states that the facility places a high priority



Clockwise from left:
Ahmed Mahmoud, Iryna Sirosh, Maya Kappil, Irina Gurvich, Qiao Wang

Another benefit of the Core Facility is that it serves as a biospecimen resource for future studies. The products stored in the facility are made available to the research community with the permission of the original study's Principal Investigator as well as Institutional Review Board approval. This provides a cost effective, efficient mechanism to utilize precious human samples. As a result, a higher volume of important research can be carried out to address diseases that seriously affect the health of communities. These include studies of environmental and genetic factors that influence risk of disease as well as identification of early biomarkers of disease. Researchers can access information about available specimens online through the Core's website. The facility has already sent stored biological specimens to over 70 different destinations from research laboratories at Columbia University to those oversees (Canada, Australia, France).

The Core Facility also provides services for researchers, such as DNA extraction, genotyping and laboratory assays. Currently, the majority of the assays run are related to exposure biomarkers, oxidative stress, and SNP genotyping. Additionally, the laboratory is equipped to perform real time PCR assays and pyrosequencing. Finally, the lab performs assays related to DNA methylation, including MethyLight assays. These services are available for a low fee to Center members. Training is also available for students and post-docs so they can run their own assays using Core equipment.

The facility is shared between the NIEHS Center for Environmental Health in Northern Manhattan and the Herbert Irving Comprehensive Cancer Center. Most of the studies associated with the center are related to cancer research, but others are related to neurological disorders and respiratory diseases.

Upcoming Events and Seminars

Spring 2011
NIEHS Center Seminar Schedule

February 17: Scott Burchiel, PhD, Professor & Chair of Pharmacogenomics, University of New Mexico, Albuquerque, NM; "Genotoxic and Non-Genotoxic Mechanisms of Immunotoxicology;" Black Building, Pharmacology Library, Rm. 724, 12:00-2:00 (part of NIEHS Center meeting).

March 11: Takehiko Nohmi, PhD, Head of the Division of Genetics and Mutagenesis, National Institute of Health Sciences, Tokyo, Japan; "Genotoxicity of Chemicals and Radiation: Tobacco, Radiation and Citrus Fruit"; Vanderbilt Clinic, 630 West 168th St., 11th floor, Room 11-242. 2:00-3:15pm.

March 17: Darryl Hood, PhD, Professor, Dept. of Neuroscience and Pharmacology, Meharry Medical College and Dept. of Pharmacology, Vanderbilt University, Nashville, TN; Title: "Polycyclic Aromatic Hydrocarbon Exposure-Induced Modulation of CNS Development, Plasticity and Behavior"; W. Duane Todd Amphitheater, P&S 16-405, 12:00-1:15pm.

March 24: James Tielsch, PhD, Professor, Dept. of International Health, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD; Title: "Indoor Air Pollution from Biomass Fuels in Low-Income Countries: Evidence for Health Effects of Interventions?" W. Duane Todd Amphitheater, P&S 16-405, 12:00-1:15pm.

HOLD THE DATE

Next Center Meeting:
Thursday, February 17th, 12-2pm
650 West 168th Street, Black Building
Pharmacology Library, Rm. 724

Dr. Scott Burchiel, Professor and Chair of Pharmacogenomics, University of New Mexico, will give a seminar titled: "Genotoxic & Non-Genotoxic Mechanisms of Immunotoxicology."

Information

Publications: Please remember to acknowledge the Center grant number **P30 ES009089** on any publications that have relevance to the goals of the Center or that have utilized the services of the Center Facility Cores.

For more information about the Center, please visit our website:
http://www.mailman.hs.columbia.edu/academic-departments/centers/niehs-center-environmental-health